POTASSIUM AND SODIUM RESTRICTION IN THE NORMAL HUMAN

Richard A. Womersley, James H. Darragh

Research Article

Find the latest version:

https://jci.me/103094/pdf

POTASSIUM AND SODIUM RESTRICTION IN THE NORMAL HUMAN [1]

By RICHARD A. WOMERSLEY [2] AND JAMES H. DARRAGH [3]

(*From the Department of Medicine, Yale University School of Medicine, New Haven, Conn.*)

Restriction of potassium intake leads to depletion of body potassium, chiefly as a result of losses of potassium in the urine (1–3). The ability of the kidney to conserve potassium has been variously assessed. Tarail and Elkinton (4) considered the renal mechanism for potassium conservation to be relatively inefficient, whereas Fourman (5) has demonstrated a U/P ratio of less than 1.0 in the normal human. Depletion of body potassium may be associated with hypokalemic alkalosis (1), shifts of sodium into potassium depleted cells (6) and retention of sodium in the extracellular phase with expansion of the extracellular fluid (1, 2).

The following experiments were designed to study the effects on the composition of the serum and urine, in normal humans, of 1) restricted potassium intake alone, and 2) restriction of sodium and potassium concurrently. External balances of water and electrolytes were observed, and internal balances of sodium, potassium, and water were calculated. Clearances of endogenous creatinine were calculated.

EXPERIMENTAL PROCEDURES AND METHODS

Three studies were carried out on two normal male subjects. Studies RW[1] and RW[2] were similar in design. Each was divided into an Initial period when sodium and potassium intakes were maintained at normal levels, a Depletion (K) period when potassium intake was restricted, a Depletion (Na and K) period when both sodium and potassium intakes were restricted (in RW[1] 9 gm. of ammonium chloride were administered on the last day of this period), and a Reloading period when sodium and potassium were returned to the diet. Study JD was divided into an Initial period, a Depletion (Na and K) period when both sodium and potassium intakes were restricted, and a Depletion (K) period when so-

dium was restored to the diet but potassium restriction was continued.

Blood samples were drawn, without stasis, under oil at the beginning and end of each period and at intermediate points. After clotting, they were centrifuged for 15 minutes and the serum drawn off. Urine was collected in 24-hour periods under mineral oil and toluol and kept refrigerated until analyzed. Stools for each period were collected, carmine red markers being used, and preserved by the addition of sulfuric acid. The subjects were weighed daily at 9 a.m. in the postabsorptive state.

Serum was analyzed for sodium, potassium, inorganic phosphorus, carbon dioxide, chloride, total proteins, and creatinine. Urine was analyzed for sodium, potassium, ammonia, titratable acid, chloride, phosphorus, carbon dioxide, pH, creatinine, and nitrogen. Feces were analyzed for sodium, potassium, chloride, and nitrogen.

The basic diet for study RW[1] was Mead Johnson's Laboratory Product No. 412[4]. This product contains the solids from milk, rendered low in sodium and potassium, with added Dextri-maltose®. Four hundred and fifty-four grams of this product, which contained 15 mEq. of potassium, were made up in distilled water for each day's basic diet. In order to lower this figure for potassium, the solution was treated with an ion-exchange resin in the ammonium cycle (except on the last three study days) and an aliquot was analyzed for sodium, potassium, and nitrogen. By this means the basic dietary potassium intake was reduced to between 2 and 3 mEq. per day.

The basic diet for studies RW[2] and JD was Mead Johnson's Laboratory Product No. 412A.[4] This is similar to Product No. 412 except that 454 gm. provided approximately 1 mEq. of potassium and 1 mEq. of sodium. Both diets were adequate in calories and nitrogen and provided 8 mEq. of chloride per day. In all studies supplements of sodium and potassium, as the chloride salts, were added to the basic diets in the Initial periods and in the other periods, as indicated previously, to give the daily intakes indicated in Table I. Additional calcium chloride was given in study RW[1] only. Two hundred extra grams of glucose were taken daily in all studies, except on day 14 of study RW[2] when only 78 gm. were taken. Distilled water was allowed *ad lib*.

External balances of water were calculated from the weight of the diet, the measured fluid intake, the weight lost in excreta, the urine volume, the changes in body

TABLE I

Daily intake and excretion of electrolytes and analyses of serum

Study	Period	Day	Weight	Intake H₂O	Na	K	Cl	N	Urine Vol.	Na	K	NH₄	TIA*	HCO₃	P	Cl	N	pH	ToA†	Serum Na	K	Cl	CO₂	P	Prot.
			kg.	ml.	mEq.	mEq.	mEq.	gm.	ml.	mEq.	mEq.	mEq.	mEq.	mEq.	mg.	mEq.	gm.		mEq.	mEq./L.	mEq./L.	mEq./L.	mM/L.	mg. %	gm. %
RW¹	Initial	1	82.17	3,000	175	51	227	11.8	1,960	122	80	76	39	—	1,109	204	18.0	5.5	115	143	4.1	102	24.3	3.5	6.9
		2	81.31	3,000	176	50	227	11.6	1,445	100	71	74	29	0.4	824	177	12.9	5.6	103						
		3	81.62	3,000	175	49	245	10.5	2,152	157	73	75	26	0.7	555	249	12.0	5.6	101						
	Depletion (K)	4	81.40	3,000	175	2	207	10.6	990	54	47	72	25	0.2	667	114	9.5	5.5	97	140	3.8	105	27.3	3.6	7.3
		5	81.62	3,000	175	2	198	10.3	1,730	78	42	78	24	0.8	659	137	12.6	5.8	102						
		6	81.71	3,200	175	2	198	11.5	2,055	93	41	78	21	1.2	600	146	10.9	5.8	99						
		7	81.97	3,150	175	2	180	11.0	1,720	88	30	83	28	0.9	736	137	10.7	5.8	111	141	3.3	104	29.5	3.0	6.5
		8	81.99	3,200	175	2	198	11.0	1,750	102	27	81	12	1.8	308	156	10.3	6.1	93						
		9	82.15	3,000	176	2	180	12.0	1,920	129	23	81	15	2.3	541	170	10.4	6.1	96						
		10	82.15	3,050	175	2	180	11.2	1,310	90	33	81	33	1.4	508	144	9.0	6.1	97						
	Depletion (Na and K)	11	82.24	3,050	3	2	26	11.2	2,680	102	24	91	19	3.8	616	150	11.8	6.3	110	144	3.1	107	28.9	3.0	6.7
		12	81.22	3,000	4	3	8	12.0	2,470	54	20	77	17	4.0	578	94	10.4	6.2	94						
		13	80.35	3,000	3	3	8	12.2	1,909	36	10	73	10	4.9	393	55	11.5	6.6	83	143	2.9	100	29.5	3.3	7.5
		14	80.25	3,000	3	2	178	11.5	1,905	29	11	103	21	2.5	834	65	12.2	6.2	124						
	Reloading	15	80.14	3,450	175	164	360	11.5	1,225	18	6	118	16	0.5	376	183	11.9	5.8	134	143	3.2	105	25.1	3.2	7.0
		16	80.95	3,000	176	167	342	12.7	1,445	242	46	137	18	0.5	231	395	12.1	5.7	155						
		17	81.34	3,000	177	167	342	12.7	2,140	285	66	118	13	0.6	51	447	12.2	5.5	131						
		18	80.84	3,000	176	167	342	12.7	2,020	240	101	95	12	0.3	26	410	11.5	5.3	107						
		19	80.60	3,000	176	167	342	12.7												132	4.6	102	27.0	4.0	7.1
RW²	Initial	1	83.92	2,800	173	82	261	12.7	2,085	219	94	69	27	1.4	559	330	13.6	5.7	96	141	4.6	105	26.8	3.3	6.5
		2	82.53	3,000	173	82	261	12.7	1,807	190	85	58	7	9.1	120	279	10.7	5.6	65						
		3	82.41	3,000	173	82	261	12.7	1,560	103	66	62	14	0.5	129	203	10.9	5.5	76						
	Depletion (K)	4	82.99	3,500	173	1	180	12.7	2,350	78	38	66	26	1.4	644	132	12.0	5.7	92	140	3.6	102	27.7	3.6	6.8
		5	82.85	3,000	173	1	180	12.7	1,480	93	36	58	15	2.1	398	129	12.1	6.1	73						
		6	82.95	3,000	173	1	180	12.7	1,905	103	32	57	11	3.4	337	155	11.7	6.4	68						
		7	82.94	3,000	173	1	180	12.7	2,425	129	27	57	12	6.6	412	146	11.9	6.2	73						
		8	82.54	3,000	173	1	180	12.7	1,350	116	20	57	15	2.4	423	139	10.6	6.3	72	137	3.6	102	29.9	3.3	6.5
		9	82.60	3,000	173	1	180	12.7	2,105	169	17	63	15	4.6	520	169	11.5	6.2	78						
		10	82.46	3,000	173	1	180	12.7	1,480	105	16	61	13	2.6	383	132			74						
	Depletion (Na and K)	11	—	2,900	1	1	8	12.7	2,060	84	10	64	10	4.2	319	103	11.1	6.3	74	144	3.3	102	30.2	3.1	6.8
		12	82.38	2,500	1	1	8	12.7	1,880	38	6	34	4	6.7	127	49	11.6	6.6	38						
		13	81.20	2,500	1	1	8	12.7	1,400	24	10	63	15	2.3	496	36	11.1	6.2	78						
	Reloading	14	80.98	3,200	173	163	342	12.7	845	58	15	61	13	0.6	262	105	11.9	5.9	74	138	3.1	102	28.0	3.2	7.0
		15	82.14	3,100	173	163	342	12.7	2,050	211	47	94	16	0.6	92	332	12.5	5.5	110						
		16	81.97	3,000	173	163	342	12.7	1,615	266	92	86	15	0.3	38	408	11.8	5.3	101						
		17	81.66	3,000	173	163	342	12.7	1,775	185	93	73	21	0.2	104	312	11.9	5.2	94						
		18	81.33	2,500	173	163	342	12.7												139	4.6	100	27.3	3.3	7.1
JD	Initial	1	85.00	2,500	173	82	261	12.7	1,810	174	89	49	33	0.7	824	262	12.7	5.5	82	134	4.1	105	26.1	3.4	7.1
		2	84.59	2,700	173	82	261	12.7	2,350	188	118	45	19	0.6	324	331	11.0	5.4	64						
		3	83.89	2,600	173	82	261	12.7	1,520	103	97	41	24	0.3	565	195	12.0	5.4	65						
	Depletion (Na and K)	4	83.47	2,800	1	1	8	12.7	2,195	61	23	48	31	0.9	896	83	14.9	5.7	79	141	4.3	106	27.8	3.0	7.1
		5	83.20	2,500	1	1	8	12.7	1,640	11	15	38	21	0.7	646	21	11.7	5.9	59						
		6	82.71	2,800	1	1	8	12.7	1,720	5	12	50	19	1.0	511	15	13.3	6.1	69						
		7	82.59	2,500	1	1	8	12.7	1,780	1	7	55	18	2.2	557	12	12.6	6.0	70						
		8	82.27	2,500	1	1	8	12.7	1,445	2	12	55	23	1.1	639	10	13.2	6.2	78	144	3.6	104	25.6	3.4	7.5
		9	82.31	2,500	1	1	8	12.7	1,880	2	12	55	15	2.9	444	8	13.4	6.1	70						
		10	82.00	2,500	1	1	8	12.7	1,675	2	12	54	21	1.6	556	5	13.6	6.1	75						
	Depletion (K)	11	81.92	2,800	173	1	180	12.7	1,070	3	7	50	16	0.7	464	14	12.8	6.0	66	134	3.4	102	25.8	3.6	7.2
		12	82.72	3,000	173	1	180	12.7	1,080	36	16	60	16	0.3	585	60	13.0	5.7	71						
		13	82.94	2,500	173	1	180	12.7	1,410	106	17	63	29	0.7	728	131	14.0	5.7	92						
		14	83.12	2,500	173	1	180	12.7	1,610	114	14	58	19	0.8	451	143	11.9	5.8	77						
		15	83.00	2,500	173	1	180	12.7												142	3.2	104	26.6	2.3	6.7

* TIA = Titratable Acid.
† ToA = Total Acids (NH₄ + Titratable Acid).

weight, and the water of oxidation of foodstuffs (1). Other balance data were calculated by methods previously reported from this department (7, 8) and by Darrow (9). No account was taken of electrolyte lost in the blood samples drawn and in the sweat.

Inorganic phosphorus was determined by the method of Fiske and Subbarow (10), modified for use with the photoelectric colorimeter; creatinine by the method of Hare (11); fecal chloride by the open Carius method (12); urine, fecal, and food nitrogen by the macro-Kjeldahl method (13); urine pH and titratable acidity were determined with the Cambridge Research Model pH-meter, urine being titrated to pH 7.4. In preparing food and feces for the determination of sodium and potassium, the "wet" ashing method was used (14) and determinations were made on the flame photometer. Serum and urine sodium, potassium, and chloride, and serum carbon dioxide and proteins were determined by methods previously reported from this department (15, 16). Urine ammonia was determined by the method of Conway (17) and urine carbon dioxide by the Van Slyke manometric method (18).

RESULTS

The results of the analyses of serum are shown in Table I. In all studies concentrations of potassium in the serum fell as potassium depletion developed. During the Depletion (K) periods of studies RW[1] and RW[2], the hypokalemia was associated with moderate increases in concentrations of bicarbonate. The highest concentrations reached were 29.5 mEq. per L. and 30.2 mEq. per L., respectively. This effect was abolished in study RW[1] by the ingestion of 9 gm. of ammonium chloride on day 14 of that study, and in study RW[2] was modified by the the restriction of sodium intake in the Depletion (Na and K) period (days 11 and 14). During the Reloading periods serum potassium concentrations returned to normal values in both studies.

In study JD the hypokalemia induced in the Depletion (Na and K) period was not accompanied by an increase in serum bicarbonate (days 4 to 11), nor did this occur when sodium was returned to the diet in the Depletion (K) period (days 11 to 15), although serum potassium continued to fall.

Serum inorganic phosphorus concentrations did not vary consistently.

The daily excretion of electrolytes and the changes of urinary pH and body weight are shown in Table I. When potassium was withdrawn from the diet its excretion fell sharply at first but shortly approached a more or less steady rate. In RW[1] after three days of depletion it had fallen from 73 mEq. per day to 33 mEq., where it remained approximately for four days. In RW[2] it fell somewhat more slowly from 66 mEq., but seemed to be flattening out in the last three days to between 20 and 16 mEq. In both experiments withdrawal of sodium was attended by a further reduction of potassium excretion. Although the total quantities of potassium in the urine were small, the breaks in the excretion curve when sodium was withdrawn are sharp enough to make them significant. Their significance is enhanced by the results of experiment JD. In this experiment the initial simultaneous withdrawal of sodium and potassium resulted in a greater and more rapid reduction of potassium excretion than did withdrawal of potassium alone in the other experiments. After the first three days the excretion had fallen to 12 mEq. per day and for five days it varied from 12 to 7 mEq. When sodium was again given it rose to 17 mEq. At no time in any of these periods was the concentration of potassium in the urine less than that in the serum.

The most outstanding features of the Depletion periods were that the urine became more alkaline and the excretion of bicarbonate tended to rise. This was true even in study JD in which serum carbon dioxide did not increase. The excretion of ammonia and titratable acid did not change significantly during the Depletion periods, but during the Reloading periods of studies RW[1] and RW[2] ammonia excretion increased, resulting in an increased output of Total Acid (ammonia plus titratable acid). The administration of ammonium chloride on day 14 of study RW[1] increased ammonia excretion on that day but had no discernible effect on potassium excretion.

During the Depletion (K) periods of studies RW[1] and RW[2] sodium and chloride excretion decreased slightly. The balance data show that these ions were retained in the body in those periods (Table II).

Phosphorus excretion decreased markedly during the Reloading periods of studies RW[1] and RW[2].

The external and internal balance data are shown in Table II. Fecal losses were taken into account in calculating the external balances of

TABLE II

Balances of water and electrolytes

Study	Period	Dura-tion	External					Extracellular			Intracellular		
			H₂O	Na	K	Cl	N	H₂O	Na	K	H₂O	Na	K
		Days	L.	mEq.	mEq.	mEq.	gm.	L.	mEq.	mEq.	L.	mEq.	mEq.
RW¹	Initial	3	−1.0	+146	− 52	+ 69	−9.4	0	− 49	− 5	−1.0	+195	− 47
	Depletion (K)	7	+0.6	+569	−267	+351	+2.5	+2.6	+444	− 5	−2.0	+125	−262
	Depletion (Na and K)	4	−2.1	−235	− 63	−154	−1.9	−1.0	−146	+ 1	−1.1	− 89	− 64
	Reloading	4	+0.4	− 89	+431	− 52	+0.3	+0.2	−172	+26	+0.2	+ 83	+405
RW²	Initial	3	−1.0	0	− 19	− 33	+1.5	+0.3	+ 94	−13	−1.3	− 94	− 6
	Depletion (K)	7	−0.8	+417	−226	+249	+4.5	+2.2	+409	+ 2	−3.0	+ 8	−228
	Depletion (Na and K)	3	−1.3	−149	− 40	−165	+3.0	−1.8	−353	− 8	+0.5	+204	− 32
	Reloading	4	+0.5	− 47	+376	+201	−0.2	+2.3	+347	+38	−1.8	−394	+338
JD	Initial	3	−1.4	+ 38	− 70	− 20	−0.1	−0.3	−126	+ 2	−1.1	+164	− 72
	Depletion (Na and K)	7	−1.7	− 84	−113	−108	−6.7	−0.2	−194	−15	−1.5	+110	− 98
	Depletion (K)	4	+1.2	+421	− 49	+357	−2.8	+3.0	+547	+ 4	−1.8	−126	− 53

electrolytes and nitrogen. The external balances of potassium have been corrected for nitrogen. Negative external balance of potassium occurred during the Depletion periods. The major part of these losses was provided from cell potassium. When sodium was present in the diet, potassium depletion resulted in marked retention of sodium in the extracellular compartment and expansion of this compartment in all studies (Depletion (K) periods). The expansion of the extracellular space was due chiefly to the transfer of cell water. Restriction of sodium intake prevented, or tended to abolish, these effects (Depletion (Na and K) periods). During the Reloading periods in studies RW¹ and RW² large positive intracellular balances of potassium occurred.

The clearances of creatinine did not change significantly in any of the studies. The electrocardiographic records remained normal. Each subject experienced one attack of diarrhea in the Depletion (Na and K) periods, and the boredom of the diet produced irritability, fatigue, and difficulty in concentration.

DISCUSSION

Deficits of potassium amounting to 330 mEq., 266 mEq., and 162 mEq., respectively, were induced in the three studies. The total exchangeable potassium of the body, which probably accurately reflects the metabolically active potassium pool (19), has been estimated to have a mean value of 46.3 mEq. per kg. of body weight (20). If this estimate is correct the subjects lost approximately 9 per cent, 7 per cent, and 4 per cent of their exchangeable body potassium. While much larger deficits have been observed in experimental studies in which depletion was induced by the ingestion of an ion-exchange resin (21), our results are comparable to those that others have obtained by dietary restriction (1, 2).

Since potassium losses in the feces were small, the deficits were due almost entirely to losses in the urine. The longest Depletion period for potassium was 11 days. While the importance of renal leakage in determining depletion of body potassium has been stressed (4), the kidney is capable of conserving potassium to a considerable extent (5). This conservative process is promoted by restriction of sodium. This is best illustrated in study RW², where the rate of excretion averaged 82 mEq. per day in the Initial period, and 9 mEq. per day on the last three days of potassium and sodium restriction. None of the subjects achieved potassium balance. The difference in the renal capacity to conserve sodium and potassium is illustrated by the Depletion (Na and K) period of study JD. On the fourth day of that period sodium had virtually disappeared from the urine, while considerable losses of potassium continued throughout the study.

It has been assumed that the small increase in serum bicarbonate recorded during the Depletion (K) periods of studies RW[1] and RW[2] represent a metabolic alkalosis, since it has been shown that in similar circumstances the CO_2 tension of alveolar air does not increase (1). The failure of alkalosis to develop during the Depletion (Na and K) period of study JD may have been due to the smaller losses of potassium that occurred in this study, or to the depletion of body sodium and potassium (Table II). Darrow, Schwartz, Iannucci, and Coville have demonstrated the dependence of serum bicarbonate on cell composition (6). They showed that bicarbonate varied inversely with cell potassium and directly with cell sodium; and, furthermore, that for every 3 potassium ions discharged from the cells 2 sodium ions were gained. It has been suggested that hydrogen may replace the one-third of potassium not "covered" by sodium (22). This theory envisages that the extracellular alkalosis so determined is balanced by an intracellular acidosis. An alternative explanation of the alkalosis of hypokalemia was advanced following the demonstration by Berliner, Kennedy, and Orloff (23) that potassium and hydrogen are in competition for a common component of the distal renal tubular cation exchange mechanism. It was postulated that the alkalosis might be due to increased hydrogen excretion. The data presented here show that during the development of the alkalosis associated with potassium depletion the urine became more alkaline, with increased excretion of bicarbonate and no increase in the excretion of acid. We feel that this is in direct contravention of the theory of the renal origin of the alkalosis, the development of which must involve shifts by way of the cellular ion-exchange mechanism. Other investigators have arrived at the same conclusion (1).

Potassium depletion resulted in the retention of salt and water in the extracellular space. Correlation between creatinine clearance and these phenomena was not demonstrated. There is no reason for excluding the possibility of some remote effect of the cellular exchanges on reabsorption of sodium by the kidney. The prompt reaction to the deprivation of sodium favors such a remote origin rather than a purely renal response.

The sharp falls in the urinary excretion of phosphorus during the Reloading periods in studies RW[1] arid RW[2] may indicate that phosphorus was being retained in the body at those times. Since the serum inorganic phosphorus levels did not change consistently, some phosphorus may have entered cells with potassium. Retention of phosphorus during the reloading of potassium-depleted subjects has been described by other workers (1, 2).

SUMMARY

1. In the normal human, restriction of potassium intake leads to a deficiency of the ion, chiefly due to urinary losses, although the kidney is able to conserve potassium to some extent.

2. Conservation of potassium is promoted by restriction of sodium.

3. Withdrawal of potassium is accompanied by a metabolic alkalosis and the production of a more alkaline urine.

4. When sodium is present in the diet, potassium depletion results in the retention of salt and water in the extracellular space. These effects are prevented or abolished by sodium restriction.

REFERENCES

1. Black, D. A. K., and Milne, M. D., Experimental potassium depletion in man. Clin. Sc., 1952, 11, 397.
2. Blahd, W. H., and Bassett, S. H., Potassium deficiency in man. Metabolism, 1953, 2, 218.
3. Reimer, A., Schoch, H. K., and Newburgh, L. H., Certain aspects of potassium metabolism. J. Am. Dietet. A., 1951, 27, 1042.
4. Tarail, R., and Elkinton, J. R., Potassium deficiency and the role of the kidney in its production. J. Clin. Invest., 1949, 28, 99.
5. Fourman, P., The ability of the normal kidney to conserve potassium. Lancet, 1952, 1, 1042.
6. Darrow, D. C., Schwartz, R., Iannucci, J. F., and Coville, F., The relation of serum bicarbonate concentration to muscle composition. J. Clin. Invest., 1948, 27, 198.
7. Elkinton, J. R., and Winkler, A. W., Transfers of intracellular potassium in experimental dehydration. J. Clin. Invest., 1944, 23, 93.
8. Elkinton, J. R., Winkler, A. W., and Danowski, T. S., Transfers of cell sodium and potassium in experimental and clinical conditions. J. Clin. Invest., 1948, 27, 74.

9. Darrow, D. C., The retention of electrolyte during recovery from severe dehydration due to diarrhea. J. Pediat., 1946, 28, 515.

10. Fiske, C. H., and Subbarow, Y., The colorimetric determination of phosphorus. J. Biol. Chem., 1925, 66, 375.

11. Hare, R. S., Endogenous creatinine in serum and urine. Proc. Soc. Exper. Biol. & Med., 1950, 74, 148.

12. Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry. Vol. 2, Methods. Baltimore, The Williams & Wilkins Co., 1932, p. 835.

13. Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry. Vol. 2, Methods. Baltimore, The Williams & Wilkins Co., 1932, p. 516.

14. Hald, P. M., Determinations with flame photometer in Methods in Medical Research, ed. by M. B. Visscher, Vol. IV, Chicago, Year Book Publishers, Inc., 1951, pp. 94–5.

15. Hald, P. M., Determinations with flame photometer in Methods in Medical Research, ed. by M. B. Visscher, Vol. IV, Chicago, Year Book Publishers, Inc., 1951, p. 79.

16. Elkinton, J. R., and Taffel, M., Prolonged water deprivation in the dog. J. Clin. Invest., 1942, 21, 787.

17. Conway, E. J., Microdiffusion Analysis and Volumetric Error. Revised, London, C. Lockwood, 1947, p. 357.

18. Peters, J. P., and Van Slyke, D. D., Quantitative Clinical Chemistry. Vol. 2, Methods. Baltimore, The Williams & Wilkins Co., 1932, p. 290.

19. Schwartz, W. B., and Relman, A. S., Metabolic and renal studies in chronic potassium depletion resulting from overuse of laxatives. J. Clin. Invest., 1953, 32, 258.

20. Corsa, L., Jr., Olney, J. M., Jr., Steenburg, R. W., Ball, M. R., and Moore, F. D., The measurement of exchangeable potassium in man by isotope dilution. J. Clin. Invest., 1950, 29, 1280.

21. Fourman, P., Depletion of potassium induced in man with an exchange resin. Clin. Sc., 1954, 13, 93.

22. Cooke, R. E., Segar, W. E., Cheek, D. B., Coville, F. E., and Darrow, D. C., The extrarenal correction of alkalosis associated with potassium deficiency. J. Clin. Invest., 1952, 31, 798.

23. Berliner, R. W., Kennedy, T. J., Jr., and Orloff, J., Relationship between acidification of the urine and potassium metabolism. Effect of carbonic anhydrase inhibition on potassium excretion. Am. J. Med., 1951, 11, 274.